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Pulmonary atresia with intact ventricular septum; second heart field derived developmental clues for myocardial and coronary artery pathology

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Introduction - Pulmonary atresia with intact ventricular septum (PAIVS) is a severe cardiac malformation that is ductus dependent and needs immediate postnatal care. The pathology concerns variable degrees of hypoplasia and hypertrophy of the right ventricle including tricuspid valve pathology. The pulmonary valve is atretic which may have been preceded, in the fetal stage, by pulmonary stenosis. Severe coronary anomalies, characterized by ventriculo-coronary arterial communications(VCAC) are found in 30% of the patients. Current cardiac developmental data show that the right ventricular (RV) myocardium is derived from the second heart field (SHF). Its anterior part contributes this myocardium to the RV outflow tract and is also employed by the neural crest cells (NCC) that enter the heart. The posterior SHF provides the epicardium derived cells (EPDC) that are important for myocardial wall compaction and formation of the coronary vasculature. We hypothesize that PAIVS without VCACs is primarily based on anterior SHF directed outflow tract septation anomalies including NCCs, while PAIVS with VCACs have a major problem related to an EPDC contribution.
Methods - We studied human fetal and neonatal postmortem specimen with known clinical diagnostic data. For our immunohistopathological evaluation we used antibodies that reveal a possible role for EPDC as well as myocardial and vascular wall differentiation markers.
Results - We showed that the presence of coronary arterial wall pathology in VCACs and concurrent coronary arterial interruptions could be present already in the fetal stage and predisposed in these cases to development from pulmonary stenosis to pulmonary atresia. Normal main coronary arteries in combination with endocardial fibroelastosis of the RV were the hallmark of a second category. We are currently evaluating a difference in myocardial pathology between both groups.
Conclusions - The above findings supported our hypothesis that PAIVS with VCAC form a primary disease that is distinct from the cases with PAIVS and endocardial fibroelastosis and normal main coronary arteries. Developmentally they can be considered as two different diseases that might need separate treatment protocols. Study of family history might reveal whether PAIVS with and without VCACs are genetically linked which can direct further developmental studies.